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Case Report

High-dose-rate brachytherapy for prostate cancer in a previously radiated patient with polyethylene glycol hydrogel spacing to reduce rectal dose: Case report and review of the literature

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ABSTRACT

PURPOSE: To describe the use of a temporary spacer to reduce rectal dose prior to prostate radiation in a man with prior pelvic radiotherapy and review the relevant literature.

METHODS AND MATERIALS: A healthy 57-year-old man presented with high-risk prostate cancer (Gleason score of 8, prostate-specific antigen level [PSA] 12.6 ng/mL, T3a by magnetic resonance imaging [MRI]), only 2.5 years after a low anterior resection followed by pelvic chemo-radiotherapy to 50.4 Gy for a locally advanced rectal cancer. Due to the prior radiation, he was not felt to be a candidate for surgery or external beam radiation, so he chose long-term androgen deprivation therapy (ADT) plus high-dose-rate brachytherapy to 36 Gy in 6 fractions. To reduce the radiation dose to the anterior rectal wall, 10 mL of a polyethylene glycol hydrogel spacer was injected between the prostate and rectum and created between 1.4 and 1.5 cm of separation along the length of the prostate.

RESULTS: Two randomized trials demonstrating that local therapy plus ADT improves overall survival compared to ADT alone provided the rationale for additional prostate radiotherapy in this otherwise healthy patient. Salvage brachytherapy is associated with a 3.4% rate of rectal fistula among the 251 cases reported in the literature from 2000–2007, with rates as high as 12% in one series. The spacer allowed the rectal dose constraint goals to be easily met.

CONCLUSIONS: Injecting an absorbable polyethylene glycol hydrogel to separate the prostate and rectum appears to be associated with decreased maximum and mean rectal doses, and may have particular utility in previously irradiated patients.

Keywords: Prostate cancer; Salvage radiotherapy; Hydrogel; Spacer

Case report

Presentation

The patient is a physically fit 57-year-old gentleman who had been diagnosed with a rectal cancer 3 years before presentation, for which he underwent a low anterior resection showing a pT3N0 tumor with negative margins but extramural venous invasion. The patient underwent adjuvant capecitabine chemotherapy plus pelvic radiation of 45 Gy in 1.8 Gy fractions followed by a rectal boost to a total dose of 50.4 Gy, all of which was completed 2.5 years before the presentation.

Eighteen months before the presentation, his routine prostate-specific antigen (PSA) was 2.6 ng/mL, but 8 months before the presentation, it rose to 8.5 ng/mL, which prompted an ultrasound-guided biopsy that was negative. PSA continued to rise to 12.6 ng/mL at 4 months before presentation, prompting a second biopsy that revealed Gleason $4 + 4 = 8$ prostate cancer in 1 of 12 cores. Digital rectal

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Conflicts of interest: None.

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examination was negative. A 3-Tesla endorectal coil MRI revealed a 25 cc prostate with intermediate T2 signal, restricted diffusion, and early enhancement at the left base consistent with prostate cancer with extracapsular extension. The left seminal vesicle was thickened but not definitely involved. In addition, in the anterior gland from mid to apex, there was a 1.9 × 1.5 cm focus highly suspicious for prostate cancer with anterior extracapsular extension.

The patient was evaluated by an experienced urologic oncologist who felt that with the extent of disease, surgery was not a good option because it was likely noncurative and would pose a high risk of complications owing to the prior pelvic radiation.

Therapeutic plan

After multidisciplinary consultation, the patient elected to proceed with a long-term (2–3 years) androgen deprivation therapy (ADT) plus radiation in the form of high-dose-rate (HDR) prostate brachytherapy delivered over two implants in a conformal fashion to target the prostate and areas of extracapsular disease. Given that additional radiation dose to the rectum would put the patient at risk for rectal injury and potentially colostomy, he elected to travel to the Department of Urology, University of Heidelberg, Germany, for placement of a polyethylene glycol (PEG) hydrogel spacer (SpaceOAR; Augmenix Inc., Waltham, MA, USA) between the prostate and rectum that is intended to absorb in about 6 months but has not yet been approved by the Food and Drug Administration in the United States.

Injection of hydrogel

Ten milliliters of spacer hydrogel were injected from a transperineal approach with transrectal ultrasound guidance and under intravenous sedation. The patient was positioned in lithotomy position. The injection needle (18G) was inserted perineally and carefully driven to the space between Denonvilliers' fascia and the anterior rectal wall. To create enough space for the spacer gel and to ensure steady dispersion, the space was dissected, using 25 mL of injectable saline (''hydrodissection''). After ensuring the correct position of the needle and suitable space, the hydrogel was administered. The distance of rectal wall to prostate/Denonvilliers' fascia was measured before and after spacer hydrogel injection and showed a gain of 14–15 mm owing to the spacer hydrogel (Fig. 1), which could be confirmed on MRI. An axial T2-weighted image of the patient's prostate and rectal area before and after spacer injection are shown in Fig. 2. The total intervention time for spacer injection was 5 min.

HDR brachytherapy procedure

The patient received 2 months of neoadjuvant ADT before the procedure. Consistent with two previous reports from the University of California at San Francisco (UCSF) of patients who received HDR monotherapy for prostate cancer after prior pelvic radiation, we delivered 36 Gy in six fractions of 6 Gy each, which is estimated to be biologically equivalent to a dose of 72 Gy in 2 Gy daily fractions (1, 2). Two separate implants were performed. After each

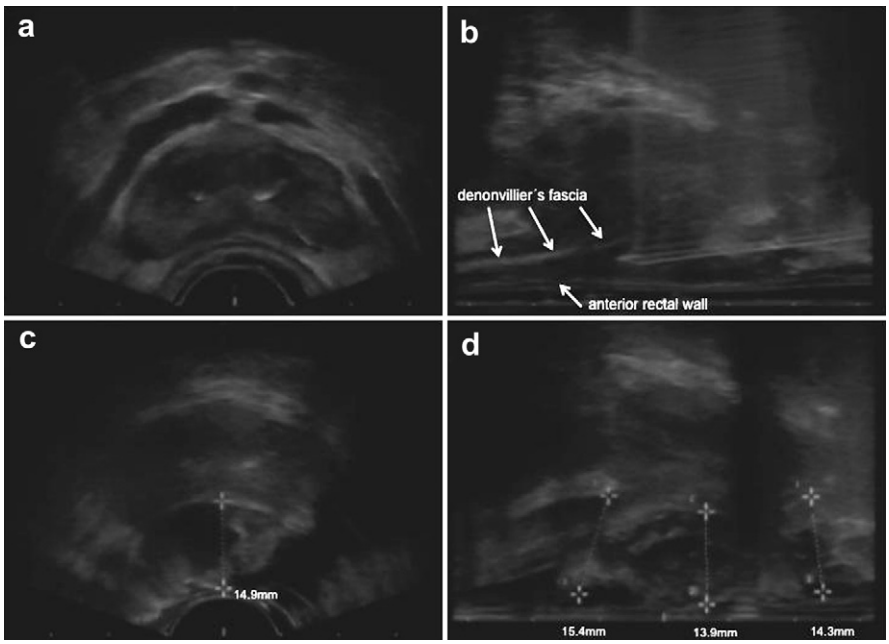

Fig. 1. Transrectal ultrasound images of prostate before (a) and after (c, d; axial and sagittal) hydrogel injection and (b) showing hydrodissection to open up the space between Denonvilliers' fascia and anterior rectal wall.

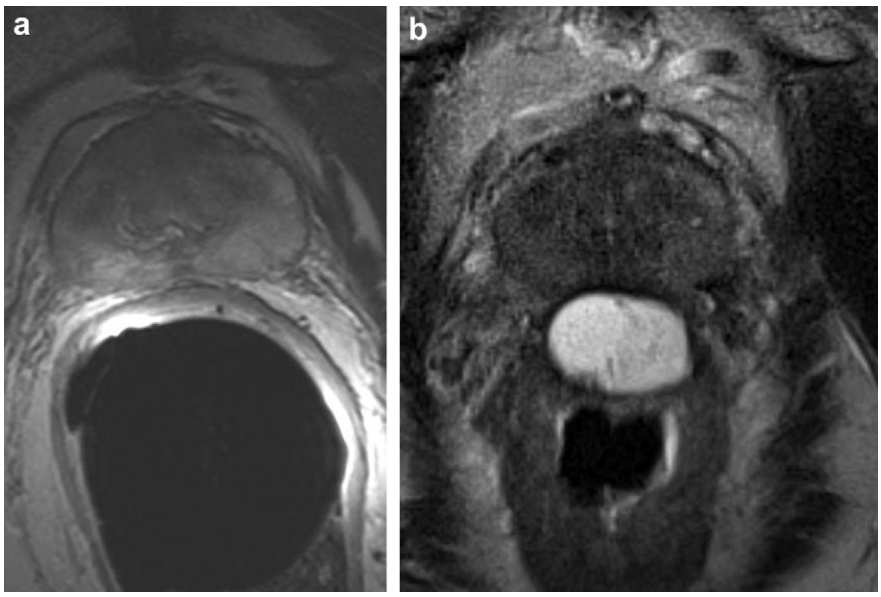

Fig. 2. (a) T2-weighted axial endorectal coil MRI before spacer injection showing almost no separation between prostate and rectum. (b) T2-weighted axial MRI after spacer injection showing new separation between prostate and rectum.

implant, the patient received an afternoon fraction the same day, followed by a morning and afternoon fraction 6 h apart on the next day. Catheters were placed throughout the prostate and into the left seminal vesicle, and then inverse planning simulated annealing was performed to deliver 6 Gy per fraction to the prostate planning target volume, while minimizing dose to the urethra, rectum, and bladder.

Impact of spacer on dosimetry

As shown in Table 1, both implants met the UCSF goals of treating at least 90% of the target to 100% of the prescription dose and keeping less than 1 cc of the urethra above 120% of the prescription dose. To get adequate coverage on the left seminal vesicle and left base, 1.2 cc of the bladder was allowed to receive 75% of the prescription dose, slightly exceeding the 1 cc goal. However, there was a dramatic dosimetric decrease in the rectum owing to the spacer. Although the goal was to keep less than 1 cc of the rectum to 75% of the dose, there were 0 cc of rectum receiving 75% of the dose, as seen in Fig. 3, where the 75% isodose line is entirely within the spacer and does not touch the rectum. A small amount of the rectum was within the 50% isodose line, and the radiation dose to the hottest 2 cc of the rectum was approximately 3 Gy per fraction.

Table 1
Desired and achieved dosimetric parameters

UCSF goals	Target PTV $V_{100} > 90\%$	Urethra $V_{120} < 1$ cc	Bladder $V_{75} < 1$ cc	Rectum $V_{75} < 1$ cc
Implant 1	97	0.4	1.2	0
Implant 2	92	0.48	1.2	0

UCSF = University of California at San Francisco; PTV = planning target volume; V_{100} = percent volume of the structure receiving 100% of the prescription dose.

Followup

The patient had no urinary frequency, nocturia, or hematuria. Nine months after implant, the patient developed mild rectal bleeding which was eventually treated with argon plasma coagulation at month 12.

Discussion

Prostate cancer treatment options after prior pelvic radiotherapy

For men who develop prostate cancer after prior pelvic radiotherapy, the available treatment options are limited (3). Most of the world's literature on the subject is from men who received prior radiation for prostate cancer (typically to a dose of approximately 70 Gy) and then recurred. Major approaches that have been attempted with curative intent include radical prostatectomy, brachytherapy, and cryotherapy. Performing a salvage radical prostatectomy in a radiated field can be difficult and lead to high complication rates. Series have reported up to a 67% rate of some degree of incontinence (4), 15% rate of rectal injury (5), and 29% rate of bladder neck stricture (4). Of all 531 cases of salvage prostatectomy that had been published in the English literature from 1990 to 2007, the rate of incontinence was 41%, rectal injury was 4.7%, and bladder neck stricture was 24% (3). Cryotherapy is not widely used as a first-line option for the definitive treatment of prostate cancer, and it is unknown whether its efficacy would be similar to surgery or radiotherapy. In the postradiation setting, cryotherapy has been associated with up to a 96% rate of incontinence (6), a 55% rate of urethral sloughing (6), 55% rate of bladder stricture (7), 44% rate of perineal pain (8–10), and 11% rate

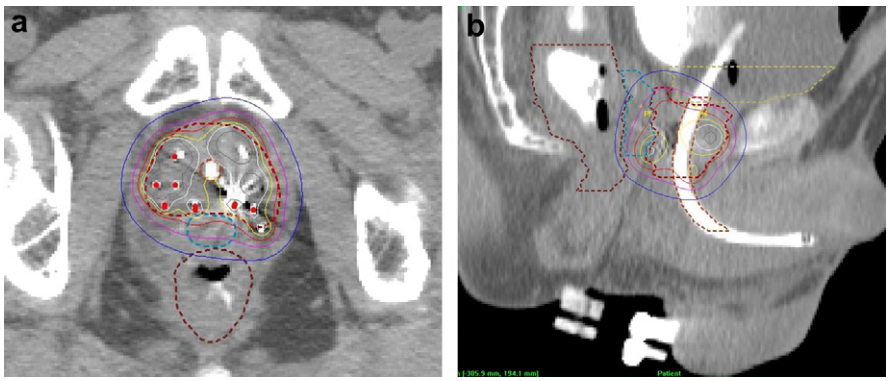

Fig. 3. (a) Axial image of high-dose-rate (HDR) plan. Prostate (*red*), spacer (*light blue*), and rectum (*brown*) are contoured. None of the rectum is exposed to the 75% isodose line (*purple*), which is contained entirely in the spacer. A small portion of the anterior rectum is exposed to the 50% isodose line (*dark blue*—outermost isodose line). (b) Sagittal image of HDR Plan. Prostate (*red*), spacer (*light blue*), and rectum (*brown*) are contoured. None of the rectum is exposed to the 75% isodose line (*purple*—second-outermost isodose line), which is contained entirely in the spacer. A small portion of the anterior rectum is exposed to the 50% isodose line (*dark blue*—outermost isodose line).

of fistula (7). Of the 510 cases of salvage cryotherapy reported from 1990 to 2007, a weighted average of morbidity yields a 36% rate of incontinence, a 11% rate of urethral sloughing, 17% rate of bladder stricture, 36% rate of perineal pain, and 2.6% rate of fistula (3). Salvage brachytherapy after prior radiotherapy has also been reported, either as low-dose-rate seed implantation or HDR implantation of empty catheters into which a highly active radioactive source is placed for precise amounts of time to create the appropriate dose distribution. Salvage brachytherapy has been associated with up to a 31% incontinence rate (11), 24% Grade 3 or 4 rectal toxicity rate (12), 47% Grade 3–4 urinary toxicity rate (13), and 12% rate of rectal fistula requiring colostomy (12). Of the 251 cases of salvage brachytherapy reported in the literature from 1990 to 2007, the weighted average rate of incontinence was 6%, Grade 3–4 rectal toxicity was 5.6%, Grade 3–4 urinary toxicity was 17%, and fistula was 3.4% (3).

Local therapy improves survival when added to ADT

This particular patient presented with extracapsular extension, Gleason score of 8, and PSA level of 12.6 ng/mL. Given the patient's good overall health state and long life expectancy, we felt that some type of local treatment was important, in light of the two recent randomized trials showing that for patients with locally advanced prostate cancer, local radiation plus ADT improves overall survival compared with ADT alone. Specifically, the Scandinavian Prostate Cancer Group (SPCG)-7/Swedish Association for Urologic Oncology (SFUO)-3 trial randomized 875 men with locally advanced prostate cancer (78% of men had T3 disease) to ADT ± radiation and found that radiation cut the relative risk of death by 32% among men with a 10-year minimum life expectancy (overall mortality at 10 years was 39.4% vs. 29.6% favoring the combined modality arm) (14). Similarly, the Intergroup trial (National Cancer Institute of Canada-Clinical Trials Group [NCIC-CTG], Southwest Oncology Group [SWOG], Medical Research Council of the United Kingdom [MRC-UK], INT: T94-0110; NCT00002633) presented by Warde *et al.* (15) at ASCO 2010 randomized 1205 men with locally advanced disease and found that the addition of radiation to ADT reduced the relative risk of death by 23%.

HDR as monotherapy in the de novo and salvage settings

There is both a radiobiologic and dosimetric rationale for considering HDR brachytherapy for prostate cancer. The α/β ratio of the prostate has been commonly estimated to be less than 2, and certainly lower than that of the rectum, which suggests that the hypofractionation achievable with HDR can provide a radiobiologic advantage in terms of improved tumor control with less or equal risk of rectal toxicity (16–19). In addition, although a posteriorly placed permanent LDR seed cannot be retracted, HDR dosimetry is much more forgiving of the placement of catheters because dose can be optimized after placement, which is particularly important in the salvage setting where minimizing dose to the rectum is critical.

Currently, HDR brachytherapy is not widely used as monotherapy for patients with a new diagnosis of prostate cancer, although there are prospective series as well as Phase II trials evaluating it. Martinez *et al.* (20) of William Beaumont reported on the first series of 41 patients treated with HDR monotherapy to a dose of 3800 cGy treated in four fractions of 950 cGy delivered twice a day over 2 days. They found excellent dosimetric coverage of the gland with good urethral and rectal sparing and a low rate of short-term morbidity. Martin *et al.* (21) of Germany also used the same regimen on 52 patients and reported good dosimetry with minimal acute toxicity. In addition, Corner *et al.* (22) reported on a Phase II trial from the United Kingdom that includes 110 men with locally advanced disease treated with HDR monotherapy to doses of 34 Gy in four fractions, 36 Gy in four fractions, or 31.5 Gy in three fractions. The rate of acute urinary retention requiring catheterization was 6.4%,

and there were no PSA relapses with a median followup of 30 months (34 Gy), 18 months (36 Gy), and 11.8 months (31.5 Gy). Also, Yoshioka *et al.* (23) has reported on a Japanese series of 112 men treated with hormonal therapy and HDR monotherapy to 54 Gy in nine fractions over 5 days in which the 5-year PSA failure-free survival was 83% despite more than one-half of the patients having high-risk disease. Finally, *Mark et al.* (24) of Lubbock, Texas have presented in abstract form on their large series of 312 HDR monotherapy patients treated to 4500 cGy in six fractions to the prostate and seminal vesicles given as two implants of three fractions each, spaced 4 weeks apart. None of the patients received ADT, and with a median followup of 8.2 years, the PSA failure-free survival was 84.6%.

In the setting of prior pelvic radiation, UCSF investigators have published two series using a regimen of 36 Gy in six fractions given as three fractions per implants, with the implants being spaced 1 week apart. The first series by Lee *et al.* (1) in 2007 detailed 21 patients who had received prior external beam radiation (19) or LDR brachytherapy (2) for prostate cancer and developed a biopsy-proven local recurrence at an average of 5.25 years after initial radiation. Nine of the patients had extracapsular extension or seminal vesicle invasion. Eleven received neoadjuvant ADT before salvage HDR. The 2-year PSA failure-free survival was 89% and the maximum gastrointestinal toxicity was only Grade 2, but the median followup was only 18.7 months. The second series by Jabbari *et al.* (2) was of 6 patients who developed prostate cancer after receiving a prior abdominopelvic resection. All had received prior pelvic radiotherapy to a median dose of 45 Gy (range, 21–73.8 Gy). With a median followup of 26 months (range, 14–60months), no patient had experienced a biochemical recurrence, and none had higher than a Grade 3 acute toxicity, although 1 patient developed a urethral stricture that required dilation.

Predictors of fistula after salvage brachytherapy

Rectal fistula is a very rare complication of primary brachytherapy in patients who have not received prior radiation (25). However, it has been reported in 3.4% of the 251 cases of salvage brachytherapy reported in the literature from 1990 to 2007. The Dana–Farber Phase I/II study identified an interval to reirradiation of less than 4.5 years as a risk factor for developing a fistula, which placed our patient at higher risk because his interval to reirradiation was only 2.5 years. However, no dosimetric risk factors for fistula have been identified in this setting, and therefore the goal was to keep the rectal dose as low as possible.

Clinical utility of rectal spacers

The rapid dose falloff with both HDR and LDR brachytherapy mean that a small amount of space between the prostate and rectum can potentially greatly lower the rectal dose. Thus far, the literature has suggested that space created by absorbable biomaterials between the prostate and rectum can potentially lead to a reduction in acute toxicity. In 2007, Prada *et al.* (26) reported on 27 patients in whom a hyaluronic acid injection created a median of 2 cm of space between the prostate and rectum without causing acute side effects and led to a 28% reduction in the maximum rectal dose during an HDR brachytherapy boost. The same group performed a clinical trial of 69 patients receiving LDR monotherapy in which the 36 patients who received the spacer had a significantly lower risk of rectal mucosal damage at the planned proctoscopic examinations (5% vs. 36%, $p < 0.002$) (27). The group from Cancer Centers of Irvine has reported on 10 patients who had a median of 1.3 cm of space from a cross-linked hyaluronan gel spacer before HDR brachytherapy (2200 cGy) with supplemental intensity-modulated radiation therapy (IMRT) (5040 cGy) and found no Grade 1, 2, or 3 acute diarrhea, compared with 29.7% among historical controls ($p = 0.04$) (28). The same group also reported on 30 patients who received the same gel spacing and found that those patients reported an improved Expanded Prostate Cancer Index Composite Bowel Bother scores ($p = 0.03$) compared with controls who did not receive the spacer (29).

A recently published study by Noyes *et al.* (30) reported on the investigational use of human collagen to increase the distance between the prostate and the anterior rectal wall. Before the start of a course of 75.6 Gy IMRT for prostate cancer, 11 patients were injected through a transperineal approach with 20 mL of human collagen into the perirectal space, resulting in mean separation between the prostate and anterior rectum of 12.7 mm with a mean reduction in dose to the anterior rectal wall of 50%. All patients denied any rectal symptoms during the study.

More recently PEG has been used to increase distance between the rectum and the prostate. Noyes *et al.* (30) have suggested that PEG or hydrogel products may have advantages over hyaluronic acid for this application because hyaluronic acid appears to be more viscous and may not distribute as evenly and may be susceptible to radiation degradation (31).

Tokita *et al.* (32) from the Cancer Center of Irvine reported on the use of a PEG spacer as a viable means to enhance rectal dose sparing. Twenty-four combined HDR brachytherapy and IMRT patients were administered the spacing material in the prostate rectal interspace transperineally at the time of catheter implantation. Results showed an increase in the mean prostate rectal spacing of 0.8–0.9 cm and an average decrease in rectal V_{70} from 41.4% to 33.6% with a maximum rectal dose decrease of 36.6%. The same group reported on 34 patients treated with either HDR brachytherapy plus IMRT or IMRT alone who were administered PEG to generate a 1.0 cm mean separation between the prostate and rectum, resulting in a decrease in the maximum and mean rectal dose by 11.5% and 30.0%, respectively with rectal wall V_{70} decreasing by 19.8%, respectively (33).

The group from Johns Hopkins injected PEG into 10 cadavers and were able to generate 1.25 cm of space between the prostate and rectum, which reduced the

theoretical rectal V_{70} from IMRT from 19.9% to 4.5% ($p < 0.05$) (34).

Pinkawa *et al.* (35) reported on pilot study results from a single site (Aachen) of a multisite investigation of a PEG spacing biomaterial. Before receiving IMRT in doses up to 78 Gy in 2 Gy fractions, 18 patients were injected with the hydrogel under ultrasound (transrectal ultrasound) guidance after dissecting the space between the prostate and rectum with saline. Injecting the hydrogel resulted in a prostate to rectum distance of 10 ± 4 mm at the base, 9 ± 3 mm in the midplane, and 11 ± 7 mm at the apex. The portion of the rectum within the 75 Gy, 70 Gy, and 60 Gy isodose was decreased by 76%, 59%, and 36% on average, respectively.

Summary and conclusions

Patients who develop a local recurrence or a new diagnosis of prostate cancer after prior pelvic radiotherapy have few good options for local salvage therapy. Salvage brachytherapy has been associated with a risk of rectal complications, including fistula. PEG hydrogel was used in the current case to create 1.5 cm of space between the prostate and rectum, allowing the rectal dose to be significantly lower than previously published dosimetric goals with HDR salvage brachytherapy. Prostate−rectal spacing with absorbable spacer material may allow for safer administration of salvage brachytherapy in select patients with locally recurrent prostate cancer or a new diagnosis after prior pelvic radiotherapy.

Acknowledgments

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